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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,084	10/24/2001	Avi J. Ashkenazi	GENE 2630PIC66	4358

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EXAMINER

BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 11/13/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/017,084

Applicant(s)

ASHKENAZI ET AL.

Examiner

David J Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-77 is/are pending in the application.
- 4a) Of the above claim(s) 1-57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 58-77 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 and 7.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Claims 1-57 have been cancelled in Paper No.1.5, filed 10/24/2001.
2. Claims 58-77 are pending and under examination.

Priority

3. If applicant desires priority under 35 U.S.C. 119(e), 120, 121 and 365(c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____," should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the

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application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior applications under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

Specification

4. The disclosure is objected to because of the following informalities:

a. The ATCC address on page 372 needs to be updated to:

10801 University Boulevard, Manassas, VA 20110-2209.

b. The disclosure is objected to because it contains an embedded hyperlink

and/or other form of browser-executable code on page 311, line 33. Applicant is

required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 58-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 58-77 are indefinite because the protein identified as PRO337 is a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed nucleic acid encodes a protein that comprises an "extracellular domain" (for example see claim 58 parts (c) and (d)) is indefinite, as the

art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal sequence" (claim 58, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

b. Claims 71-73 are indefinite for reciting "hybridizes" in claim 71 or "hybridization occurs under stringent conditions" in claim 72 because the exact meaning of the term or phrase is not clear. It is not clear what full set of conditions are encompassed in the claims. The specification discloses several conditions on pages 73-74 as well as "high stringent" and "moderately stringent" it is not clear which if any of these conditions are required for the claims.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 58-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide encoded by the polynucleotide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polynucleotides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed

above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides comprising the sequence set forth in SEQ ID NO: 522, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 58-62, 70-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell line containing cDNA deposited under ATCC accession No. 209487. It is not clear that the cDNA deposited as ATCC no. 209487 is known and publicly available or can be reproducibly isolated from nature without undue experimentation or is the same as SEQ ID NO:522 or contains additional sequences in addition to SEQ ID NO:522.

Applicant's referral to the deposit of the cDNA on page 372 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the

biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

10. Claims 58-62, 71-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 58-62, 71-77 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA encoding SEQ ID NO: 523 and DNA of SEQ ID NO: 522 and DNA of ATCC no. 209487 with completion of the deposit requirement, does not reasonably provide enablement for DNA's that are 80%, 85%, 90%, 95% or 99% ^{to DNA encoding SEQ ID # 523} and do not encode for the polypeptide of SEQ ID NO: 523. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. LRP

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity

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of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polynucleotides having at least 80%, 85%, 90%, 95% or 99% nucleic acid sequence identity to the polynucleotide of SEQ ID NO:522 or the nucleotide encoding SEQ ID NO:523 or the extracellular domain thereof as well as to polynucleotides that hybridize to such polynucleotides. There is no functional limitation in the claims as far as to the polynucleotide that encodes the polypeptide. Applicants have taught the polypeptide consisting of the extracellular domain or, more accurately, the mature form of SEQ ID NO:523, as well as the putative signal sequence (approximately amino acids 1-28 of SEQ ID NO:523, Figure 222). This polypeptide is disclosed to be homologous to human neurotrimin (see page 215) and is a newly identified member of the IgLON sub family of the immunoglobulin superfamily (see page 179). The specification discloses the polypeptide was positive in a proliferation of rat utricular supporting cell assay and in a chondrocyte re-differentiation assay (see pages 347 and 351). The specification does not teach an activity for the polypeptide or any active regions of the polypeptide. Thus one would not know if the polynucleotide with the claimed homology would function as a polypeptide of SEQ ID NO:523.

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use, or the polynucleotides, which encode these polypeptides. While the specification suggests that the polypeptide of SEQ ID NO:523 is homologous to human neurotrimin, what related function it possesses is undisclosed. Since PRO337 is a secreted protein, it would be expected

that the mature form would be sufficient for function in the absence of the secretory signal. The functional domain of the protein is the mature form. Knowledge of one neurotrophin protein structure and function does not provide predictability about function of a structurally related protein, even within the same class.

There are no working examples of polypeptides or polynucleotides less than 100% identical to the polypeptide SEQ ID NO:523 or the polynucleotide of SEQ ID NO:522 or the mature form thereof. The skilled artisan would not know how to use non-identical polypeptides or polynucleotides on the basis of teachings in the prior art or specification. Even if the claimed polynucleotides and polypeptides encoded thereby had a function, the specification does not provide guidance for using polynucleotides related to (i.e., 80%-99% identity) but not identical to SEQ ID NO:522 or the polypeptide of SEQ ID NO:523. The claims are broad because they do not require the claimed polynucleotide and the encoded polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

It is well known in the art that even a single modification or substitution in a protein sequence can alter the protein's function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or

glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Claims 71-73 encompass nucleotides that hybridize to those claimed in (a) to (g), however, the claims do not recite under what full set of conditions are used for hybridization or if the nucleic acid hybridizes to the full length DNA. In addition, it is unclear what the polynucleotides that do not encode SEQ ID NO: 523 and hybridize to SEQ ID NO: 522 would be used for.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Struyk et al (The Journal of Neuroscience 15(3): 2141-2156, 1995, Ids # 3).

The claims recite an isolated nucleic acid that hybridizes to a nucleic acid encoding the polypeptide of SEQ ID NO:523 or the nucleic acid sequence of SEQ ID NO:522, and a nucleic acid that hybridizes to a nucleic acid encoding SEQ ID NO:523 or a nucleic acid of SEQ ID NO:522 wherein the hybridization is under stringent conditions and the nucleic acid is at least 10 nucleotides.

Struyk et al teach a nucleic acid, NM_016522 (1378 bp matches out of 1679 total bp; see sequence alignment attached to the IDS filed as Paper No. 7 on 4/30/2002), which shares 99% nucleic acid sequence identity with nucleotides 214 to 1594 of SEQ ID NO: 522 with SEQ ID NO: 522 and is at least 10 nucleotides and would hybridize under the recited conditions to SEQ ID NO:522.

13. Claims 71-72 are rejected under 35 U.S.C. 102(b) as being anticipated by The 1991 Boehringer Mannheim Catalog, page 557, 1991.

The claims have been described supra.


The Boehringer Mannheim Catalog teach random primers of 6 nucleic acids and the primers would hybridize to the nucleic acids recited in claim 71 under the stated conditions.

Conclusion

14. No claim is allowed.
15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (703) 605-1200. The examiner can normally be reached at (703) 605-1200 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
703-605-1200



LARRY R. HELMS, PH.D
PRIMARY EXAMINER